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THE PATENT OFFICE J - 9 MAY 1997 LONDON

1. Your reference — N.72359 - NP

2. Patent application number *(The Patent Office will fill in this part)* — - 9 MAY 1997 — **9709494.0**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

27.8.74

07986520002

4. Title of the invention

DELIVERY DEVICE AND METHOD

5. Name of your agent *(if you have one)*

J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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GRAY'S INN
LONDON WC1R 5LX

Patents ADP number *(if you know it)*

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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b) there is an inventor who is not named as an applicant, or
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11. I/We request the grant of a patent on the basis of this application

Signature J.A. Kemp & Co - Date 9 May 1997

J A KEMP & CO

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DELIVERY DEVICE AND METHOD

This invention relates to the delivery of an agent. The invention has particular, but not exclusive, application to the delivery of one or more agents to the adventitial surface of a blood vessel at the site of an anastomosis.

Arterial bypass grafts are used to restore or improve the blood flow to tissues when the native vessels are occluded or significantly stenosed, usually by atheroma.

Of all arterial bypass grafts performed, some 15% - 30% might be expected to fail within the first 24 months, caused predominately by progressive vascular smooth muscle cell (SMC) intimal hyperplasia. This occurs mainly at the distal anastomosis and areas contiguous to it. Usually, it occurs to a lesser extent at the proximal anastomosis and along the length of the graft. In perspective, of all cardiac and peripheral arterial bypass procedures performed each year in the United Kingdom alone (approximately 25,000 - 30,000), between 5,000 - 8,000 will fail, causing a significant mortality, morbidity, requirement for "re-do" procedures and financial cost to the health services. A similar rate of failure will be seen wherever such anastomoses are constructed, including renal and visceral artery revascularisations, formation of renal dialysis access fistulae, renal and liver transplantation and arterial reconstructions following trauma.

Currently, several mechanistic approaches are used to salvage failed arterial bypass grafts, including "re-do" surgery (i.e. a further bypass graft), surgical "patch" angioplasty, balloon angioplasty (either alone or following thrombolysis) and more recently, endoluminal stenting. Each of these methods prompts further SMC intimal hyperplasia (secondary to vessel wall trauma) which may result in an even higher secondary failure rate.

Recent studies have suggested that the smooth muscle cells in the outer (media) part of the arterial wall may be

of greater importance than previously considered. Perhaps by responding to variations in the relative degrees of oxygenation across the arterial wall, these cells seem to be the first to proliferate and migrate towards the sub-endothelial space and so form the neo-intimal hyperplastic lesion seen. Whereas all currently employed treatments simply try to keep the vessel lumen patent by physical means, we consider a better approach to be the prevention of smooth muscle cell proliferation in the first instance.

Agents known for having an antiproliferative effect include heparin; anti-sense for c-myc and c-myb; ACE inhibitors; and high dose steroids.

In one use, the present invention enables agents for countering smooth muscle cell intimal hyperplasia to be applied directly to the adventitial surface of the arterial wall (i.e. closest to those cells in the outer media). Any agent used can be applied specifically at the sites most likely to develop an intimal hyperplastic lesion, since these sites are readily exposed at the time of operation.

According to one aspect of the present invention there is provided a device for use in the delivery of at least one agent to the adventitial surface of a blood vessel, the device comprising a body including at least a first substantially impermeable body portion which is shaped to in use extend longitudinally along and at least partially surround a first blood-carrying vessel, the first body portion including longitudinally spaced apart seal portions adapted to seal in use against the adventitial surface of the first blood-carrying vessel and an intermediate portion between the seal portions which is adapted to in use contain and deliver the at least one agent to the adventitial surface of the first blood-carrying vessel.

According to another aspect of the present invention there is provided a method of delivering at least one agent to at least one blood-carrying vessel, the method comprising:

positioning a device over a blood-carrying vessel at a desired site of delivery of the at least one agent;

forming a sealed reservoir between the interior of the device and the adventitial surface of said vessel at said site; and

providing in the sealed reservoir a pharmaceutical formulation containing an agent for delivery to said adventitial surface at said site.

Where appropriate, two or more agents may be delivered together.

Preferred agents which may be delivered by the devices of the invention are nucleic acids, i.e. DNA or RNA for the purposes of gene therapy. This allows delivery of the nucleic acids to the adventitia of the blood vessel. These nucleic acids may be delivered in a "naked" form unassociated with a vector, or by means of a gene therapy vector. It is preferred to deliver them by means of a gene therapy vector. The nucleic acids may be associated with the vector by means known in the art.

Any suitable gene therapy vector may be used. In particular, viral or non-viral vectors may be used.

Suitable viral vectors include recombinant adenoviruses, retroviruses, pseudotyped retroviruses, herpesviruses, vaccinia viruses and baculoviruses, having nucleic acids incorporated into their genomes which effect gene therapy.

Suitable non-viral vectors include oligonucleotides, plasmids, liposomes, cationic liposomes, pH sensitive liposomes, liposome-protein complexes, immunoliposomes, liposome-protein-polylysine derivatives, water-oil emulsions, polyethylene imines and dendrimers.

Where appropriate, two or more types of vector can be used together. For example, a plasmid vector may be used in conjunction with liposomes.

Viral vectors of the invention are preferably disabled, e.g. replication-deficient. That is, they lack

one or more functional genes required for their replication, which prevents their uncontrolled proliferation *in vivo* and avoids undesirable side effects of viral infection.

The hereinafter described and illustrated preferred embodiments of device and method allow the native vessel, arterial bypass graft and intervening anastomosis to be exposed to agents which may be expected to have an anti-proliferative effect.

Some advantages of the devices of the invention are: (i) they provide a delivery reservoir, allowing for sustained delivery; (ii) no intraluminal manipulations are required and the arterial endothelium remains intact; and (iii) the agent or agents are applied locally.

The devices of the invention may be applied to the treatment or prevention of intimal hyperplasia arising from any clinical circumstances. For example, it is possible to treat intimal hyperplasia arising after any type of surgical procedure, including angioplasty, for example balloon angioplasty; bypass surgery, such as coronary bypass surgery in which a vein or another artery is anastomosed to an artery; other anastomosis procedures, for example anastomosis in the legs; and endarterectomy, for example carotid artery endarterectomy. It is also possible to treat intimal hyperplasia associated with arterial damage or hypertension, for example pulmonary artery hypertension. The shape and size of the device is chosen accordingly, depending on the shape of the blood vessel or blood vessel/graft combination to which it is to be applied.

The invention provides for treatment of intimal hyperplasia in any type of blood-carrying vessel, e.g. in an artery or vein or graft, preferably an artery.

Preferred embodiments of devices in accordance with the present invention will now be described, by way of example only, with reference to the accompanying drawings

in which:

Figure 1 shows, in perspective view, a schematic drawing of a conventional "end-to-end" anastomosis;

Figure 2 shows, in perspective view, a schematic drawing of a conventional "end-to-side" anastomosis;

Figure 3 shows, in perspective view, a schematic drawing of a conventional "side-to-side" anastomosis;

Figure 4 shows in perspective a schematic of a first embodiment of device positioned around an end-to-end anastomosis;

Figure 5 is a longitudinal cross-sectional view in the vertical plane of Figure 4;

Figure 6 is a similar view to that of Figure 5, but showing a modified form of the first embodiment of device with an alternative construction for its seal portions;

Figure 7 shows in perspective a schematic of a second embodiment of device positioned around an end-to-side anastomosis;

Figure 8 is a longitudinal cross-sectional view in the vertical plane of Figure 7;

Figure 9 shows in perspective a schematic of a third embodiment of device positioned around a side-to-side anastomosis;

Figure 10 is a longitudinal cross-sectional view in the vertical plane of Figure 9;

Figure 11 shows in perspective a schematic of a fourth embodiment of device positioned around a side-to-side anastomosis, showing a part embedded blood vessel;

Figure 12 is a longitudinal cross-sectional view in the vertical plane of Figure 11.

By way of background, arterial bypass grafts are commonly used to restore or improve the blood flow to tissues when the native vessels are occluded or significantly stenosed, usually by atheroma. Whether using autologous vein or artery, or a synthetic material such as DACRON or PTFE, grafts are commonly anastomosed to the

native vessels in one of three ways: "end-to-end" (Figure 1); "end-to-side" (Figure 2); or "side-to-side" (Figure 3). Of these techniques, end-to-side and side-to-side are much more common than end-to-end. In Figures 1 to 3 the blood flow is represented by the arrows.

In the end-to-end anastomosis illustrated schematically in Figure 1, a graft 1 has been anastomosed to native blood vessel portions 2a,2b in end-to-end fashion. The sites of anastomoses are referenced 3 in Figure 1.

In the end-to-side anastomosis shown schematically in Figure 2, to bypass an occlusion 4 in the native blood vessel 5 a graft 6 is shown as having been anastomosed to the native blood vessel 5 at an anastomosis site 7.

In the side-to-side anastomosis shown schematically in Figure 3, the native blood vessel 8 is shown as occluded at 9. A graft 10 is also shown as having been anastomosed to the native blood vessel 8 in side-to-side fashion at anastomosis site 11.

The first preferred embodiment of device illustrated in Figures 4 and 5 is shown applied to an end-to-end anastomosis. The device comprises a generally tubular body 12 which, in use, extends longitudinally along and surrounds the blood-carrying vessel made up by the end-to-end anastomosis of a graft 13 to a native blood vessel 14.

As is most clearly visible from Figure 5, the body 12 of the device has longitudinally spaced apart seal portions 15 provided at its opposite ends. When, in use, the device is positioned over the site 16 of the end-to-end anastomosis these seal portions 15 seal against the adventitial surface of the graft 13 and native blood vessel 14.

In the embodiment of Figures 4 and 5 the radial thickness of the material of the body 12 is greater at the seal portions 15 than it is in an intermediate portion 17 of the body between those two seal portions 15.

Consequently, when the seal portions 15 seal against the adventitial surfaces of the graft 13 and vessel 14, a space is formed between the interior of the body 12 of the device and the adventitial surfaces of the enclosed ends of the graft 13 and vessel 14. This space constitutes a sealed reservoir 18 and is shown longitudinally aligned with the anastomosis 16.

This reservoir enables a pharmaceutical formulation containing one or more agents to be placed in contact with the adventitial surface of the graft and vessels 13,14 at the site of the anastomosis 16. Where the formulation is in the form of a fluid or gel it can for example be injected using a hypodermic needle and syringe, through the wall of the body 12, into the sealed reservoir 18. The agents contained in the formulation advantageously have an anti-proliferative effect to counter smooth muscle cell intimal hyperplasia at the site of the anastomosis 16 and areas contiguous to it.

The pharmaceutical formulation need not be in fluid or gel form, for example it may be a runny paste having a consistency similar to that of toothpaste; sufficiently runny as to remain in contact with the pulsing adventitial surface to which it is exposed and also not to constrict the vessel.

To position the device over the site of the anastomosis 16 the cylindrical body 12 may be slid axially over one of the graft 13 and blood vessel 14 prior to their being anastomosed. The surgeon can then join the graft 13 and vessel 14 together at the anastomosis site 16 and the body 12 may then be slid back over the anastomosis site 16 to occupy the position shown in Figure 5, whereupon to enable sealing of the seal portions 15 to the respective adventitial surfaces.

Alternatively, the body 12 of the device may, as shown, be provided with a longitudinal slit 19 along its full length. In this way the surgeon can anastomose the

graft 13 and vessel 14 without introducing the device 12 to the patient's body. Once the anastomosis has been successfully completed the surgeon can then select an appropriately sized body 12 and apply it around the anastomosed graft and vessel by opening the flexible body 12 along slit 19, slipping it over the anastomosed graft and vessel 13,14 and then sealing the opposed longitudinal edges of the body at the slit 19 together, for example using a conventional "tissue glue", such as the Thrombin Glue sold under the name TISSEAL, or a cyanomethacrylate based glue.

To concentrate the effect of the pharmaceutical formulation contained within the reservoir 18, and to avoid leakage of its agents to the surrounding tissue, the body 12 is substantially impermeable to the formulation. The material is also, advantageously, biodegradable over a set time course, for example a period of 1 to 5 days, by which time the active agents in the formulation are likely to have become exhausted. The material is also chosen so as not to promote too severe a reaction from the surrounding tissue. Examples of suitable materials for the body include gelatin, alginate or collagen. These materials also allow the body flexibility and enable the device to be manufactured by molding or extrusion.

The wall material of the body 12 may also advantageously be self-sealing so as to preserve the integrity of the sealed reservoir 18 if it is required to be punctured by a hypodermic needle. Alternatively or additionally, any leak in the wall that is revealed after removal of the needle may be sealed with "tissue glue" or the like.

A range of differently sized bodies 12 may be provided to be fitted over differently sized vessels. Lower limb vessels commonly have an external diameter of approximately 6-8 mm. Coronary vessels commonly have an external diameter of approximately 3-5 mm. Accordingly, a

range of body sizes of between about 3-10 mm diameter may be made available in sterilised packets to the surgeon. In addition, the size of the body may be varied to influence the volume of the reservoir 18. It is envisaged that a suitable size for the reservoir 18 will be up to 10 ml, preferably 2-5 ml.

To accommodate expansion of the blood-carrying vessel 13,14 caused by pulsatile blood flow therealong, at least the seal portions 15 of the body are advantageously capable of being stretched so as to accommodate expansion of the vessel walls. It is highly desirable to avoid constriction of the vessel walls by the device, whilst at the same time maintaining the seals intact.

The seal portions 15 need not be as shown in Figures 4 and 5. They may, for example, have the construction shown in Figure 6, in which the radial thickness of the material of the body 12 is constant along the length of the body, with the intermediate portion 17 being ballooned internally relative to the internal diameter of the body 12 at the seal portions 15. Both seal portions 15 are formed with tails which extend in the longitudinal direction, for example each to contact the adventitial surface of a respective one of the graft 13 and vessel 14 over a length "X" in the axial direction of approximately 8-15 mm. These long tails for the seal portions 15 can be made to act in the manner of "flap valves" to help seal the reservoir 18, although clearly no flow through the "flap valve" is desired. Alternatively, the tails could be folded inwardly (not shown) to double the thickness of the body at its ends to form seal portions of greater radial body thickness than the body thickness in the intermediate portion, in a similar fashion to what is shown in Figure 5.

To form or help form fluid tight seals the surgeon may adhere the seal portions 15 to the adventitial surfaces, for example using a glue of the sort mentioned above, for example a "tissue glue". This may not, however,

be essential. For example, if the size of the body 12 at the seal portions 15 is chosen to match the girth of the vessels 13,14 it may not be necessary to use any glue. Instead, the surgeon might rely on the radial interference between the internal diameter of the body 12 at the seal portions 15 and the diameter of the adventitial surfaces to interfere sufficiently as to create a seal without the need for glue. This is particularly so with the long-tailed seal portion embodiment of Figure 6. The seal portions should not, however, be so tight on the vessel as to constrict it.

The agents of the invention are preferably provided in the device of the invention in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier. Any suitable pharmaceutical formulation may be used.

For example, suitable formulations may include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, bactericidal antibiotics and solutes which render the formulation isotonic with the body fluids of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question. Of the possible formulations, sterile pyrogen-free aqueous and non-aqueous solutions are preferred.

Figures 7 and 8 illustrate a second preferred embodiment in which the device is used in conjunction with an end-to-side anastomosis of the general form illustrated in Figure 2.

In Figures 7 and 8 the body 20 is shown as having a first body portion 21 and a second body portion 22 branched thereto at an angle of less than 90° to form a generally Y-

shaped body. It will be appreciated that the first and second body portions 21,22 may be branched to one another at other branch angles up to and including 90°, in which latter case the body be generally T-shaped. The surgeon may advantageously have available to him a series of differently sized and differently shaped bodies from which he may choose the device most appropriate to the layout and size of the anastomosed vessels. The first body portion 21 may, for example, be approximately 1-10 cm in length, with the length of the second body portion 22 being approximately 1-5 cm in length.

The first body portion 21 is generally tubular and is shown as surrounding a native blood vessel 23. The second body portion 22 is also generally tubular and is shown as surrounding a graft 24 anastomosed to the native blood vessel 23 in end-to-side fashion at anastomosis site 29. As can be seen from Figure 8, the opposite ends of the first body portion 21 are provided with seal portions 25 and the extreme end of the second body portion 22 is provided with a seal portion 26. As in the earlier embodiment these seal portions 25,26 may advantageously be sealed to the adventitial surfaces of the blood vessel 23 and graft 24 respectively using a "tissue glue".

Figure 8 shows a sealed reservoir 27 formed between the interior of the first body portion 21 and the adventitial surface of the blood vessel 23, with this reservoir 27 extending into the interior of the second body portion 22. This sealed reservoir 27 is thus aligned with the site 29 of the anastomosis.

As with the earlier embodiment, the sealed reservoir 27 may advantageously be injected with a liquid pharmaceutical formulation containing active agents, using a hypodermic needle and syringe.

To facilitate fitment of the device to the vessel 23 and graft 24, the body 20 of the device may be provided to the surgeon in a sterilised package containing two

symmetrical halves, split in and symmetrical about the plane of the section illustrated in Figure 8. In such a case the surgeon would be required to assemble the two identical body halves together after having anastomosed the graft 24 to the vessel 23, and to seal the facing edges of the identical halves together, for example using glue as previously described.

Alternatively, only the first body portion 21 may be provided with a longitudinal slit 28, as shown in Figure 7. In this way the surgeon could slide the second body portion 22 over the end of the graft 24. The surgeon would then be able to anastomose the free end of the graft 24 to the blood vessel 23 and then slide the second body portion 22 back down the graft 24 to cover the site of the anastomosis 29, using the slit 28 to feed the blood vessel 23 into the centre of the first body portion 21 to be surrounded thereby. The surgeon could then seal to one another the facing longitudinal edges of the first body portion 21 at the slit 28 to form the sealed reservoir 27 therein.

It will be appreciated that other configurations may be used for the body portions 21 and 22. For example, the first and second body portions 21 and 22 could be provided separately from one another and be secured to one another to form the sealed reservoir 27 only when in situ in the patient.

Figures 9 and 10 illustrate a third embodiment of device suitable for use in the situation of a side-to-side anastomosis of the general form illustrated in Figure 3 of the drawings.

In Figures 9 and 10 the body 30 of the device is shown as comprising a first body portion 31, from which are branched second and third body portions 32,33. The branching of the second and third body portions 32,33 to the first body portion 31 forms a generally X-shaped body as shown in Figure 9.

All three body portions 31,32,33 are generally

tubular in shape. The device is generally similar to that illustrated in Figures 7 and 8, save for the additional third body portion 33.

First body portion 31 surrounds the occluded native blood vessel 34 and is sealed to the adventitial surface thereof by seal portions 35.

Second and third body portions 32,33 surround the graft 36 and are sealed to the adventitial surface of the graft at respective seal portions 37,38. As is most clearly shown in Figure 10, the effect of the seal portions 35,37,38 is to form a sealed reservoir 39 between the interior of the body 30 and the adventitial surfaces of the enclosed vessels, which reservoir 39 can be at least part-filled with a pharmaceutical formulation in the manner described earlier.

To facilitate fitment of the device illustrated in Figures 9 and 10 the device is advantageously provided to the surgeon in at least two parts. For example, the first body portion 31 may be provided separately of a second component comprising second and third body portions 32,33. By providing the body portions with longitudinal slits therealong (not shown), the body portions may be fitted to surround the vessel 34 and graft 36 and then be sealed along those longitudinal slits and sealed to one another along a line of contact, to provide the sealed reservoir 39 around the point of anastomosis 40.

Figures 11 and 12 show a variant of the device shown in Figures 9 and 10. In Figures 11 and 12 the same reference numerals for common parts have been used as in Figures 9 and 10. One particularly suitable use for the device of the present invention is in coronary artery bypass graft surgery. In such a situation the first blood vessel 34 may, as shown, be a coronary artery that is part-embedded in the heart wall 50. A device of the form shown in Figures 9 and 10 could not be fitted to a part-embedded coronary artery 34, as the first body portion would be

unable to extend fully around the artery 34. Accordingly, in the Figure 11 and 12 embodiment the first body portion 51 of the body 31 does not describe a full circle when viewed in cross-section transverse to its longitudinal extent; instead, it is generally arcuate. In the illustrated embodiment it describes an arc of approximately 180°. This enables the first body portion 51 to be fitted over only the exposed portion of the part-embedded coronary artery 34, to only partly surround it. In this arrangement the longitudinally extending edges 41 of the first body portion 51 are sealed by the surgeon either to the adventitial wall of the coronary artery 34 or, as shown, to the surface of the heart wall 50, for example by using tissue glue.

The Figure 11 and 12 variant of device is also applicable to other surgical procedures in which the first blood-carrying vessel is an artery part-embedded in a wall of the organ supplied by that artery, these other organs including the brain, the bladder and the uterus.

Although the illustrated embodiments have concentrated on the use of the device to deliver agents to blood-carrying vessels at sites of anastomosis as well as to sites contiguous herewith, the invention is not limited to such uses. The device may, for example, be used more generally to deliver agents to the adventitial surface of non-anastomosed blood-carrying vessels. For example, following a balloon angioplasty a device of the form shown in Figures 4-6 may be placed around the exterior of an artery in the region of the site of the balloon angioplasty, so as to deliver one or more agents thereto via the adventitial surface of the artery.

In the embodiments described above, the sealed reservoirs are shown as taking the form of a radial space or clearance between the adventitial surface of the blood-carrying vessel and the interior of at least the first body portion, which space is at least part-filled in use by a

pharmaceutical formulation. Such a space is not, however, essential. For example, in an alternative, non-illustrated embodiment the body may have a generally impermeable flexible outer layer and a flexible inner layer which is impregnated with the formulation and which is arranged to just contact the adventitial surface in use.

The outer layer may, for example, be made of solid collagen and the inner layer made of sponge-like collagen cross-linked thereto, the sponge-like layer being capable of being impregnated with the pharmaceutical formulation containing the agent to be delivered. In such a situation, the device could be provided to the surgeon for fitment with the formulation already impregnated therein, or it may be wetted with the formulation after fitment, for example by being injected as described earlier.

Alternatively, the agent may be coated onto an internal surface of the body, which surface is just in contact with the blood vessel in use. Alternatively, agent may be dispersed throughout the structure of the body.

CLAIMS

1. A device for use in the delivery of at least one agent to the adventitial surface of a blood vessel, the device comprising a body including at least a first substantially impermeable body portion which is shaped to in use extend longitudinally along and at least partially surround a first blood-carrying vessel, the first body portion including longitudinally spaced apart seal portions adapted to seal in use against the adventitial surface of the first blood-carrying vessel and an intermediate portion between the seal portions which is adapted to in use contain and deliver the at least one agent to the adventitial surface of the first blood-carrying vessel.

2. A device as claimed in claim 1, wherein at least part of the intermediate portion is arranged to be spaced from the adventitial surface of the first blood-carrying vessel in use to form a reservoir that is sealed against leakage by the seal portions and is at least part-filled by a pharmaceutical formulation containing the agent to be delivered.

3. A device as claimed in claim 2, wherein the formulation is in the form of a fluid or gel that is injectable into the reservoir or a paste.

4. A device as claimed in claim 2 or claim 3, wherein the material of the body portion is self-sealing to enable the reservoir to be injected with the fluid or gel after fitment of the device to the first blood-carrying vessel and after sealing of the seal portions to the adventitial surface of the first blood-carrying vessel.

5. A device as claimed in any one of claims 2 to 4, wherein the reservoir can contain up to approximately 10 ml of fluid, preferably at least 2-5 ml.

6. A device as claimed in any one of claims 2 to 5, wherein the thickness of the body material is generally constant along the elongate extent of the first body portion, the reservoir being formed in use by a ballooning

of the first body portion between its seal portions.

7. A device as claimed in any one of claims 2 to 5, wherein the thickness of the material of the first body portion is smaller in the intermediate portion than at the sealing portions, said reduced thickness forming the reservoir.

8. A device as claimed in any one of the preceding claims, wherein the inner surface of the first body portion comprises a "sponge-like" material which is capable of being impregnated with a pharmaceutical formulation containing the agent to be delivered.

9. A device as claimed in any one of claims 1 to 7, wherein the inner surface of the first body portion is impregnated with a pharmaceutical formulation containing the agent to be delivered.

10. A device as claimed in any one of the preceding claims, wherein the material of the body portion is biodegradable.

11. A device as claimed in any one of the preceding claims, wherein the body portion is made of gelatin, alginate or collagen.

12. A device as claimed in any one of the preceding claims, wherein the body portion is moulded or extruded.

13. A device as claimed in any one of the preceding claims, wherein the seal portions are adapted to be glued in use to the adventitial surface of the adjacent blood-carrying vessel.

14. A device as claimed in any one of the preceding claims, wherein at least the seal portions of the first body portion are flexible so as to accommodate expansion of the first blood-carrying vessel caused by pulsatile blood flow therealong.

15. A device as claimed in any one of the preceding claims, wherein each opposite end of the first body portion is formed into a long tail to form a respective seal portion.

16. A device as claimed in claim 15, wherein the elongate extent of each of the tails is approximately 8-15 mm.

17. A device as claimed in any one of the preceding claims, wherein the body of the device is generally tubular in shape whereby, in use, to surround a first blood-carrying vessel in which a graft vessel has been anastomosed to a native blood vessel in end-to-end fashion, with the intermediate portion being longitudinally aligned with the anastomosis for the delivery thereto of the agent.

18. A device as claimed in any one of claims 1 to 16, wherein the first body portion of the device is at least partly tubular and the body further includes a second generally tubular body portion which is branched to the first body portion to form a generally Y- or T-shaped body.

19. A device as claimed in claim 18, wherein the body is shaped to be applied, in use, to a first blood-carrying vessel to which a graft vessel has been anastomosed in an end-to-side anastomosis, the first body portion being arranged at least partially to surround the first blood-carrying vessel and the second body portion being arranged to surround and be sealed to the graft vessel.

20. A device as claimed in claim 19, wherein the second body portion includes a seal portion adapted to seal against the adventitial surface of the graft vessel.

21. A device as claimed in claim 19 or claim 20, wherein a reservoir which is, in use, formed within the first body portion extends into the interior of the second body portion to be generally aligned, in use, with the anastomosis for the delivery thereto of the agent.

22. A device as claimed in any one of claims 1 to 16, wherein the first body portion of the device is at least partly tubular and the body further includes second and third generally tubular body portions which, at least in use, are branched to the first body portion to form a

generally X-shaped body.

23. The device as claimed in claim 22, wherein the body of the device is shaped to be applied, in use, to a first blood-carrying vessel to which a second blood-carrying vessel has been anastomosed in a side-to-side anastomosis, the first body portion being arranged to at least partially surround the first blood-carrying vessel and the second and third body portions being arranged to surround and be sealed to the second blood-carrying vessel on different sides of the anastomosis.

24. A device as claimed in claim 23, wherein the second and third body portions each include a seal portion adapted to seal against the adventitial surface of the second blood-carrying vessel.

25. A device as claimed in claim 23 or claim 24, wherein a reservoir which is, in use, formed within the first body portion extends into the interior of the second and third body portions to be generally aligned, in use, with the anastomosis for the delivery thereto of the agent.

26. A device as claimed in any one of claims 22 to 25, wherein the first body portion is supplied as a first component and the second and third body portions are provided separately of the first component, which body portions are arranged to be assembled and sealed together in use.

27. A device as claimed in any one of claims 18 to 26, wherein the first body portion is generally arcuate in cross-section transverse to its longitudinal extent so as to enable it to surround the exposed portion of a first blood-carrying vessel when that vessel is part-embedded in tissue, and longitudinally extending edges of the first body portion are arranged to be sealed, in use, to the adventitial wall of the first blood-carrying vessel or to adjacent tissue.

28. A device as claimed in claim 27, wherein the first blood-carrying vessel is an artery that is part-

embedded in a wall of the organ supplied by that artery.

29. A device as claimed in any one of claims 1 to 26, wherein the first body portion is slit along its longitudinal extent to facilitate its fitment over the first blood-carrying vessel, the body edges of said slit being sealable together in use or sealable to the adventitial surface of the first blood carrying vessel.

30. A device as claimed in any one of the preceding claims, wherein the seal portions of the first body portion are arranged to seal against the adventitial surface of a first blood-carrying vessel of approximately 3-10 mm diameter.

31. A method of delivering at least one agent to at least one blood-carrying vessel, the method comprising:

positioning a device over a blood-carrying vessel at a desired site of delivery of the at least one agent;

forming a sealed reservoir between the interior of the device and the adventitial surface of said vessel at said site; and

providing in the sealed reservoir a pharmaceutical formulation containing the agent for delivery to said adventitial surface at said site.

32. A method as claimed in claim 31, wherein the sealed reservoir is formed by sealing the device to said adventitial surface or to surrounding tissue using "glue".

33. A method as claimed in claim 31 or claim 32, wherein the device is positioned to fully surround said vessel at said site.

34. A method as claimed in any one of claims 31 to 33, wherein said site is a site of anastomosis.

35. A method as claimed in claim 34, wherein said at least one blood-carrying vessel comprises at least two anastomosed vessels.

36. A method as claimed in any one of claims 31 to 34, wherein said site is a site of anastomosis and the adventitial vessel surface contiguous to said anastomosis

site.

37. A method as claimed in any one of claims 31 to 33, wherein said blood-carrying vessel includes an anastomosed graft and said site is a portion of said vessel displaced from a site of anastomosis.

38. A method as claimed in any one of claims 31 to 37, wherein the formulation is provided by being injected into the sealed reservoir.

39. A method as claimed in any one of claims 31 to 37, wherein the formulation is provided by placing a paste containing the formulation within the reservoir.

40. A method as claimed in any one of claims 31 to 39, wherein the device is of the form claimed in any one of claims 1 to 30.

41. A device or method as claimed in any one of the preceding claims, wherein the agent to be delivered to the adventitial surface is one for countering intimal hyperplasia at the site of an anastomosis or areas contiguous to it.

42. A device or method as claimed in any one of the preceding claims, wherein a plurality of agents are simultaneously delivered to the adventitial surface, in use.

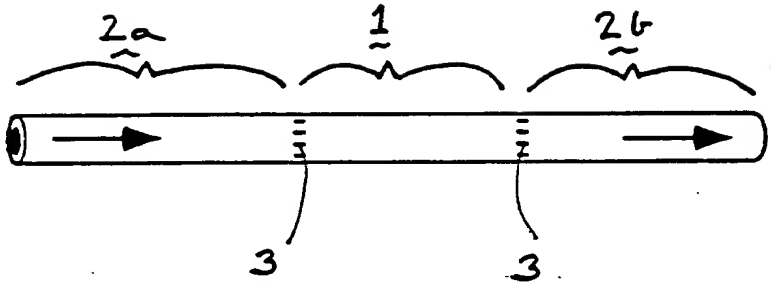


FIGURE 1

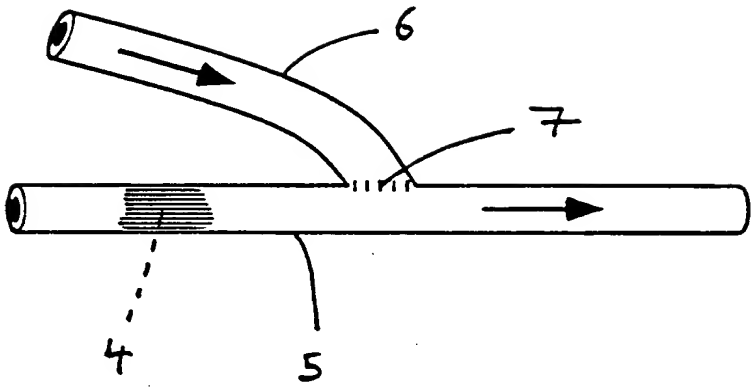


FIGURE 2

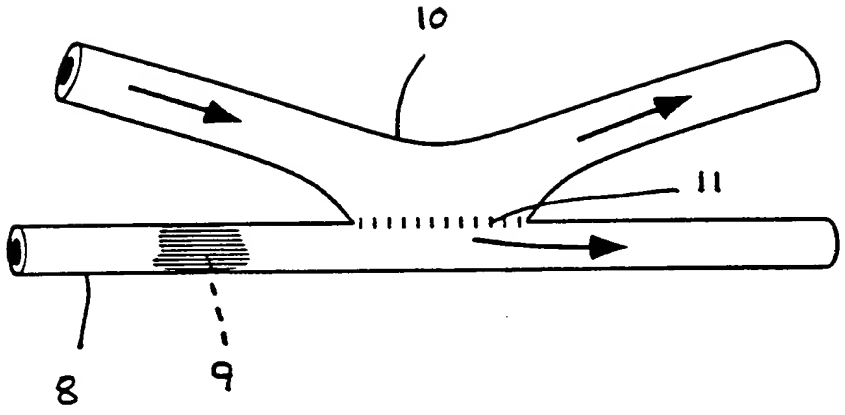


FIGURE 3

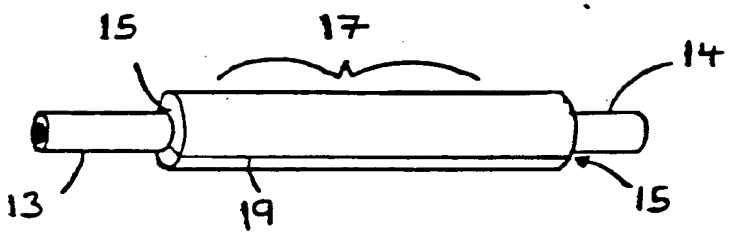


FIGURE 4

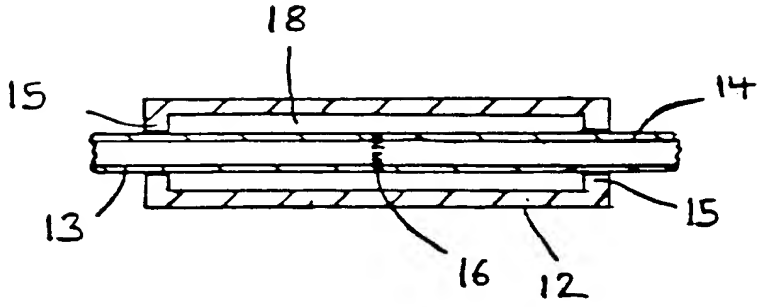
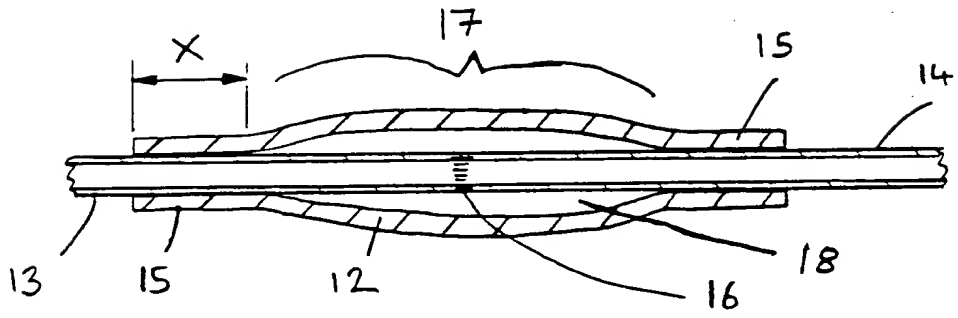


FIGURE 5



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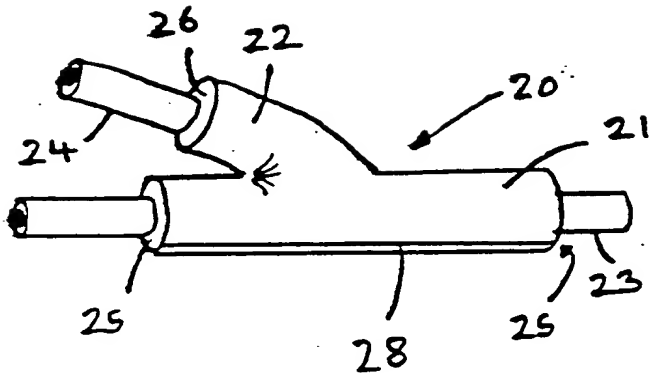

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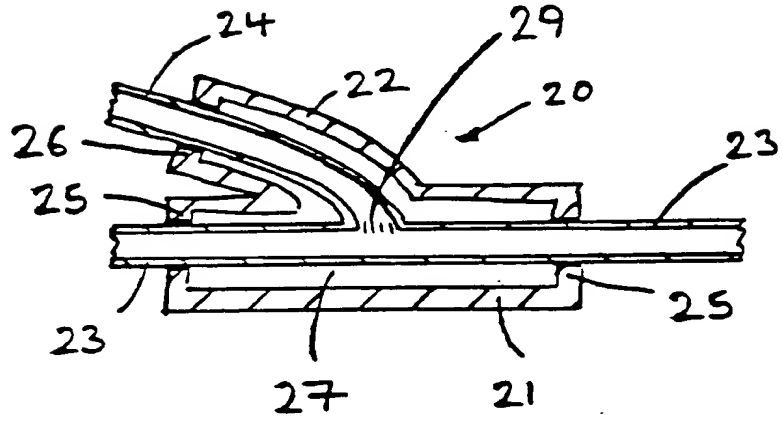

FIGURE 8

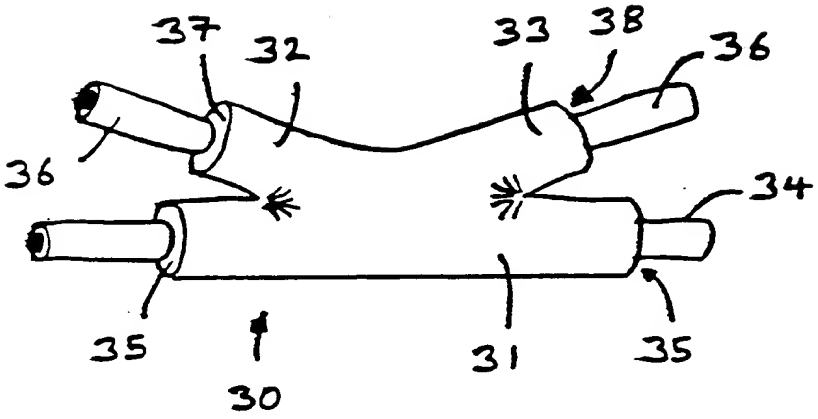

FIGURE 9

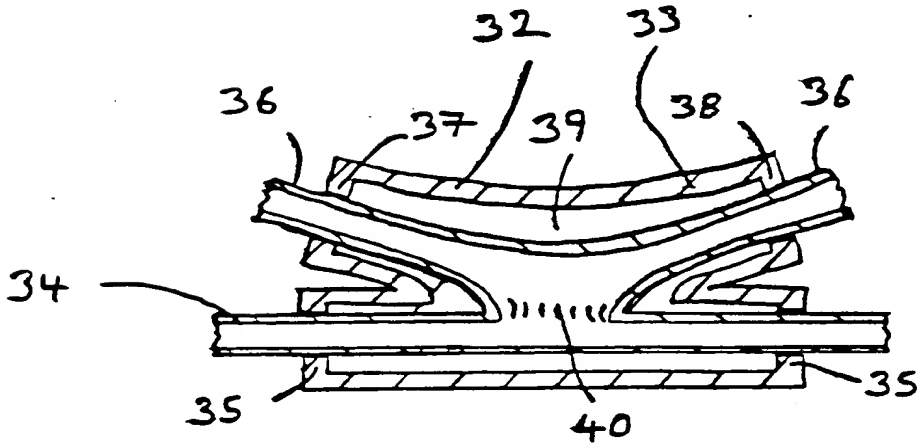

FIGURE 10

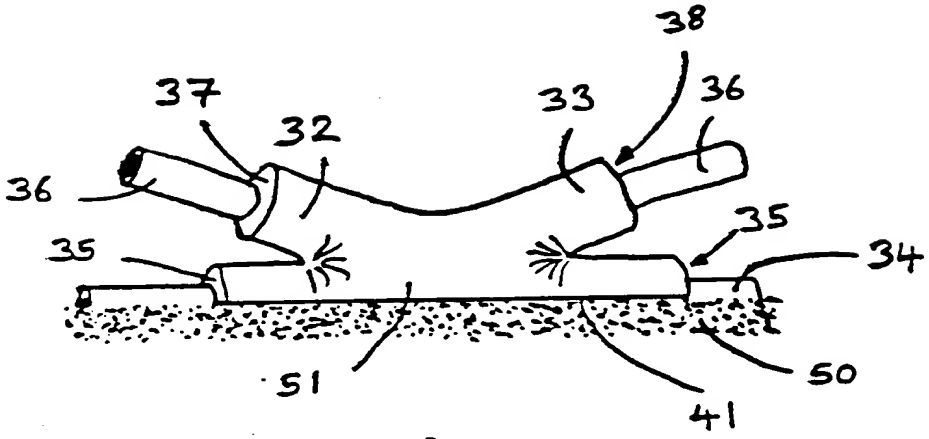

FIGURE 11

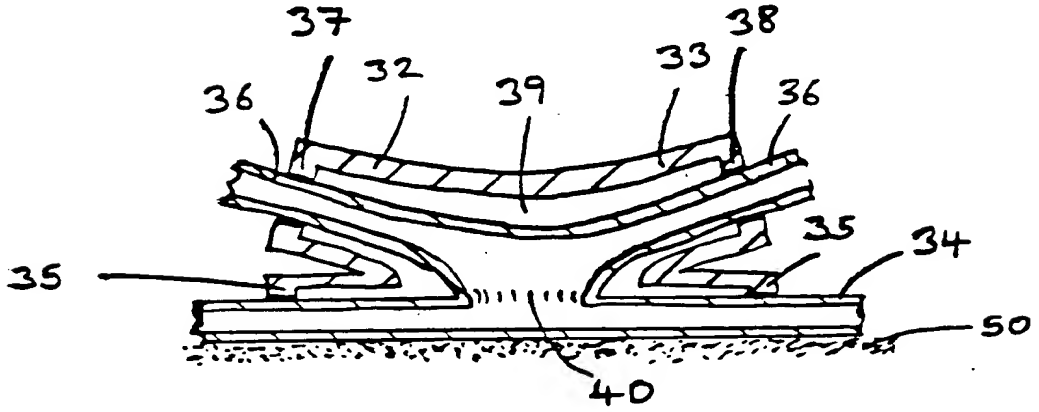

FIGURE 12